## REMARKS

Claims 15, 22-30, 34, 53, 60-68, 72, 93-97, and 99-106 have been canceled without prejudice and without acquiescence. Applicant reserves the right to prosecute claims to any canceled subject matter at any time. The claims were canceled and new claims added in order to ease the examination of the claimed subject matter. New claims 107-150 have been added. No new matter has been added.

The issues outstanding in this application are as follows:

- Claims 15, 22-25, 26-29, 34, 60-63, 64-67, 72, 93-97, 99-101 and 103-106 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described;

- Claims 15, 22-30, 34, 53, 60-68, 72, 93-97, and 99-106 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled;

- Claims 15, 22-30, 34, 53, 60-68, 72, 93-97, and 99-106 were rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite.

Applicants respectfully traverse the outstanding rejections, and Applicants respectfully request reconsideration and withdrawal thereof in light of the amendments and remarks contained herein.

## I. Summary

Applicants have cancelled all pending claims and added new claims to more clearly describe and claim the subject matter claimed in this application. Applicants reserve the right to claim other subject matter in related applications, including the subject matter of all canceled claims.

For the reasons discussed below, and that are supported by the attached Declarations by Drs. Forsberg and Hedlund, all new claims now directly address and overcome the Examiner's concerns and rejections as expressed in the Office Action of January 5, 2005. Applicants therefore, respectfully request that all rejections be withdrawn and that a Notice Of Allowance be issued.

## II. 35 U.S.C. § 112, first paragraph, written description

Claims 15, 22-25, 26-29, 34, 60-63, 64-67, 72, 93-97, 99-101 and 103-106 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described. Applicants respectfully traverse.

### A. "At least selected from..."

Claims 15, 22, 53, 60, 93 and 94 were rejected for use of the terminology "is at least selected from the group consisting of..." Without acquiescence, the new claims omit this language. Therefore, the new claims obviate the basis for this rejection.

### B. Description of Staphylococcal enterotoxin E variant

Claims 15, 22-25, 27-29, 34, 60-63, 65-67, 72, 93-97, 99-101 and 103-106 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described because the Examiner contends that the specification describes only variants of Staphylococcal enterotoxin E starting with the "base" or "backbone" structure SEA/E-18, and not wild-type Staphylococcal enterotoxin E ("seroreactivity is compared to SEA/E-18 and is only viewed as a combination of region C mutations with mutations in other regions. The specification does not teach reduced seroreactivity for individual mutations in Region C alone of SEE as is now claimed" (Office Action page 3)).

Without acquiescence and reserving all rights in and to this subject matter, the new claims now clearly describe the claimed subject matter of this application as being variants of Staphylococcal enterotoxin E, wherein the mutations of SEA/E-18, and conserved substitutions thereof, form the "base" or "backbone" sequence, from which additional substitutions are made in other regions. More specifically, as explained in the specification, for example in paragraphs 160 and 175 (and paragraphs 53-54, and 60-67 discussing conserved variants), and in the prior art of record, for example, Antonsson *et al.* 1997 and Abrahmsén *et al.*, 1995 (both of record), SEA/E-18 comprises SEE having the following amino acid substitutions, wherein the amino acid positions are relative to SEE reference SEQ ID NO: 7: amino acid position 20 is glycine or a conserved variant thereof, amino acid position 21 is threonine or a conserved variant thereof, amino acid position 24 is glycine or a conserved variant thereof, amino acid position 27 is lysine or a conserved variant thereof, and amino acid position 227 is serine or a conserved variant thereof or alanine or a conserved variant thereof.

All new and pending claims now expressly contain this subject matter. Therefore, Applicants respectfully request that this rejection be withdrawn.

**C. Antibody moiety**

Claims 26 and 63 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that is not described by the specification. The Examiner alleges that these claims failed to specify what the antibody of the conjugate binds to, and, therefore, that these claims were not supported by the written description. While not in acquiescence, and reserving all rights, all new claims expressly require that the antibody moiety be directed against a cancer-associated cell surface structure. Therefore, all new claims obviate the basis of this rejection. Therefore, Applicants respectfully request that this rejection be withdrawn.

**III. 35 U.S.C. § 112, first paragraph, enablement**

Claims 15, 22-25, 26-29, 34, 60-63, 64-67, 72, 93-97, 99-101 and 103-106 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described. Applicants respectfully traverse.

On pages 4-9 of the Office Action, the Examiner sets forth the support and arguments for the rejections of the claims based on lack of enablement. Applicants respectfully traverse. For ease of examination, Applicants respond to the Examiner's issues in the order in which they are set forth in the Office Action.

On the bottom of page 4 and top of page 5 of the Office Action, the Examiner has stated that the specification fails to teach any use for generic antibody conjugates that are not directed to cancer antigens. This was apparently directed to claims 26 and 63, since the other claims are to an antibody moiety that is directed against a cancer-associated cell surface structure. In any event, all of the new and currently pending claims are directed to antibody moieties directed to cancer–associated cell surface structures. Therefore, the basis of this rejection is obviated, and this rejection should be removed.

On pages 5-7 of the Office Action, the Examiner contends that the specification does not enable claims to variants of SEE wherein the "base" or "backbone" sequence to be modified is not SEA/E-18, for example, where it is "SEE *per se*." Without acquiescence and reserving all rights in and to this subject matter, the new claims now clearly describe the subject matter as being variants of Staphylococcal enterotoxin E, wherein the mutations of SEA/E-18, and conserved substitutions thereof, form the "base" or "backbone" sequence, from which additional substitutions are made in the present invention. As explained above for written description, the specification and prior art teach that SEA/E-18 comprises SEE having the following amino acid substitutions, wherein the amino acid positions are relative to SEE reference SEQ ID NO: 7: amino acid position 20 is glycine or a conserved variant thereof, amino acid position 21 is threonine or a conserved variant thereof, amino acid position 24 is glycine or a conserved variant thereof, amino acid position 27 is lysine or a conserved variant thereof, and amino acid position 227 is serine or a conserved variant thereof or alanine or a conserved variant thereof. Since all claims now expressly contain this subject matter, the Examiner's enablement rejections based on this issue are now overcome and moot.

Therefore, Applicants respectfully submit that all new claims are free of these enablement rejections. For example, this amendment directly overcomes the Examiner's concerns, for example as expressed on pages 5-7 of the Office Action, that SEE conjugated to

an anti-cancer antibody has little SADCC activity ("superantigen-antibody dependent cytotoxicity (SADCC) of SEE conjugates is poor;" and "[t]he art teaches that antibody conjugates with SEE have markedly decreased antibody dependent cellular cytotoxicity," page 6 of the Office Action) and that "it appears that amino acids 20-27 of SEA must be transferred to SEE and are *required to generate SADCC* in any see mutant" (page 6 of the Office Action). The claimed subject matter now has amino acids 20-27, or conserved substitutions thereof, of SEA in SEE, and the specification and prior art are clear that the SEA/E-18 has significant SADCC activity when conjugated to an antibody (unlike SEE when so conjugated) (see, for example, paragraph 160 and Antonsson et al. 1997 and Abrahmsén et al., 1995 (both of record)). Additionally, the specification has many examples of modified SEE variants that, when conjugated to an anticancer antibody, show SADCC. For example, Table 4 on page 44 shows 24 such variants.

Therefore, the new claims overcome all enablement rejections that are based upon this concern, such as those set forth on pages 5-7 of the Office Action, since the claimed subject matter uses a SEA/E-18 "backbone" or "base," and not SEE "*per se*." Therefore, these rejections should be withdrawn.

Further, on the bottom part of page 5, the Examiner contends that Cavallin *et al.* shows that the claimed combinations of amino acids are "not predictable." Applicants respectfully disagree and traverse. Applicants stress that statements in Cavallin should not be taken beyond their context. Cavallin is a paper addressed to the spectral and **thermodynamic** properties of Staphylococcal enterotoxins (that paper's entitled "The Spectral and Thermodynamic Properties of Staphylococcal Enterotoxin A, E, and Variants . . ."). It is not addressed to therapeutic properties of the molecules. The statement in Cavallin that the Examiner refers to on page 5 of the Office Action (page 1671, column 1 of Cavallin) for support of the non-enablement rejection, is **in the context** of the author's study of the spectral and **thermodynamic** properties of Staphylococcal enterotoxins, and is **not** addressed to functional properties of enterotoxins. Therefore, this statement from Cavallin is irrelevant to, and cannot support the Examiner's non-enablement argument. Thus, this lack of enablement argument should be withdrawn. The attached Declaration by Dr. Göran Forsberg, who is a coauthor of the Cavallin paper, confirms this point.

Additionally, in the middle of page 6, the Examiner states that Cavallin shows "SEE and variants thereof have a markedly reduced ability as compared to SEA to induce T-cell proliferation." As already noted by Applicants in the Amendment filed on July 18, 2003 (page 10) in this application, this position by the Examiner is incorrect. Cavallin actually shows the opposite: Cavallin shows that SEA has a **lower** ability to induce T cell proliferation of mouse lymphocytes than SEE and its variants. Specifically, in Table I on page 1668, Cavallin shows that the $EC_{50}$ value of SEE and variants thereof is lower than that of SEA. The $EC_{50}$ is well-known in the art as the concentration giving 50% of maximal effect (*See, e.g.,* Antonsson et al., *J. Immunol.* 158:4246, 1997 (of record) and the attached Declarations by Drs. Forsberg and Hedlund). The *lower* the $EC_{50}$ value, the *lower* the concentration of the substance that is required to produce a response – and, therefore, *the higher the activity* (i.e., the lower the $EC_{50}$ value, the higher the activity). As is clearly shown in Table I of Cavallin, SEE and variants thereof have lower $EC_{50}$ values than SEA. Therefore, Table I of Cavallin shows that SEE and its variants have higher T cell proliferation activity than SEA. Therefore, this basis for rejecting the claims should be withdrawn.

On the top of page 7, the Examiner states that the specification does not reasonably enable the claimed combinations of mutations within a variant based on an SEA/E-18 "backbone." The Examiner bases this concern on the asserted point that Table 1 of the specification shows that some combinations of mutations, such as SEA/E-75, "abolish the SADCC activity," and therefore the specification is not reasonably predictive of the claimed substitutions. Applicants respectfully submit that this is an incorrect interpretation of the data in Table 1. Rather, Table 1 shows that all of the 24 different combinations of mutations have varying amounts of SADCC activity. For example, mutant SEA/E-75 has 10% of the SADCC activity of SEA/E-18. As supported by the attached Declarations, the SADCC activity of SEA/E-18 is substantial, and therefore a variant having 10% of that activity still has notable SADCC activity. Indeed, the data shown in Table 1 are $LD_{50}$ values, the dose at which 50% of target cells are killed by SADCC. Therefore, a mutant like SEA/E-75, having 10% of the SADCC of SEA/E-18, means that it takes a dose that is 10 fold higher than SEA/E-18 to kill 50% of cells by SADCC. However, since the effect is still killing 50% of cells by SADCC, this value still indicates that the variant has notable SADCC activity. In certainly does not "abolish" SADCC activity.

Therefore, Table 1 of the specification teaches that various combinations of amino acids within the scope of the claimed invention produce variants having a range of SADCC activity, and always retaining at least some SADCC activity. Applicants submit that this teaching enables one skilled in the art to predict and produce variants within the scope of the present claims. This basis for arguing non-enablement should, therefore, but withdrawn.

At the top of page 7, and in more detail on pages 8-9, the Examiner supports the non-enablement rejection by arguing that there is insufficient evidence that the claimed invention would work, especially *in vivo*. Applicants respectfully traverse. As shown by the specification and the attached Declarations by Drs. Forsberg and Hedlund, there is ample evidence that the claimed invention functions to kill target cancer cells, including *in vitro* and *in vivo*.

For example, on the bottom of page 7, the Examiner questioned whether the specification teaches the full claimed scope of antibodies, or a molecule-binding antibody active fragment, that are directed against a cancer-associated cell surface structure. First, the specification amply describes and enables the complete invention using, for example, antibody fragments C215Fab and 5T4Fab, that are directed to a cancer associated cell surface antigens (see, e.g., paragraph 103). The specification also describes the use of antibodies to, for example, cell surface structures associated with cancers including cancers of the lung, breast, colon, kidney, pancreas, ovary, stomach, cervix and prostate (see paragraph 102). Specific examples of tumor markers include carcinoembryonic antigen, prostate specific antigen, urinary tumor associated antigen, fetal antigen, tyrosinase (p97), gp68, TAG-72, HMFG, Sialyl Lewis Antigen, MucA, MucB, PLAP, estrogen receptor, laminin receptor, erb B and p155 (see, e.g., paragraph 103).

Moreover, the attached Declaration by Drs. Forsberg and Hedlund show that various antibodies may be conjugated with the Staphylococcal enterotoxin variants of the present invention, and that the conjugate can successfully be used against cells expressing an antigen recognized by the antibody. For example, the data in the Declarations shows that various Staphylococcal enterotoxins of the present invention may be conjugated with various antibodies and the conjugate used successfully both *in vitro* and *in vivo*. As stated in the Declarations, the inventors attest that from the data shown, one skilled in the art would

understand that the variants of the instant invention may be conjugated with any antibody that recognizes a cell surface antigen, such as a cancer-associated antigen, and the conjugate can be successfully used both *in vitro* and *in vivo* to kill target cells expressing the cell surface antigen recognized by the antibody. The Declarations demonstrate both successful *in vitro* and *in vivo* use of variants conjugated to antibody fragments directed to various tumor markers.

Finally, on the top of page 7, and on pages 8 and 9 of the Office Action, the Examiner expresses concern as to whether to claimed conjugates function *in vivo*. The attached Declarations by Drs. Forsberg and Hedlund clearly show that the conjugates of the claimed invention function effectively *in vivo*. As explained in more detail in the Declarations, a typical variant conjugate of the claimed invention, for example 5T4FabSEA/E-120, was successfully used to treat non-small cell lung carcinoma (NSCLC) in humanized SCID mice. Applicants respectfully submit that this data shows that the claimed invention is enabled to the treatment of cancers *in vivo*. Further in support, Applicants respectfully request that the Examiner reconsider Applicants' arguments from the Amendment dated July 18, 2003, page 11 wherein Applicants provide additional reasons why the claims are enabled for *in vivo* use.

Therefore, Applicants respectfully request that this basis for the Examiner's enablement rejection be removed.

Should the Examiner criticize either of the above enablement arguments, Applicants respectfully request that the Examiner provide detailed reasons supporting such a position. In the absence of such specific support, Applicants submit that, for the reasons discussed herein, the current claims are enabled, and, therefore, all enablement rejections should be withdrawn.

**IV. 35 U.S.C. § 112, second paragraph**

Claims 15, 22-30, 34, 53, 60-68, 72, 93-97, and 99-106 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly not clearly defining the claimed subject matter. Applicants traverse.

Regarding the rejection concerning the language "is at least selected from the group consisting of ...," applicant's new claims omit this language. Therefore, the basis for this rejection is obviated.

Regarding the rejection based on the argument that the claims do not include reference to a sequence identifier, all new claims contain such a reference. Therefore, the basis for this rejection is obviated.

Finally, as to the rejection that the composition claim lacks an additional element, applicants thank the Examiner for the kind suggestion, and the claims have been amended to include an aqueous medium. Support for this subject matter may be found in paragraphs 107-138.

In view of the above arguments, Applicants have described and enabled the invention as claimed and respectfully request that all rejection be withdrawn, and that a Notice of Allowance be issued for all pending claims.

## CONCLUSION

In view of the above arguments, Applicants have described and enabled the invention as claimed and respectfully request that the rejection be withdrawn.

Applicant are enclosing a check, with this response, for the fee for a one month extension of time for a Small Entity. Applicants request a one month extension of time to file this response. Further, Applicant claims Small Entity status. If other fees are due, and/or if the attached check is inadequate, please charge any additional fees due to our Deposit Account No. 06-2375, under Order No. HO-P02188US0 from which the undersigned is authorized to draw.

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Respectfully submitted,

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